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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM32/0623

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ART UNIT	PAPER NUMBER
1641	7

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on April 30, 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 4-9, 23-27 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1, 4-9, 23-27 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☒ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

The Group and/or Art Unit location of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1641. This change is effective as of February 7, 1998.

The Office Action of December 1, 1997 is hereby vacated.

In this application:

Claim 1 was amended.

Claims 2, 3, and 10-22 were cancelled.

Claims 23-27 were added.

Claims 1, 4-9, and 23-27 are now pending and under examination.

Drawings

The drawings in this application are objected to by the Draftsperson as informal. Any drawing corrections requested, but

not made in the prior application should be repeated in this application if such changes are still desired. If the drawings were changed and approved during the prosecution of the prior application, a petition may be filed under 37 CFR 1.182 requesting the transfer of such drawings, provided the parent application has been abandoned. However, a copy of the drawings as originally filed must be included in the 37 CFR 1.60 application papers to indicate the original content.

Claim Objections

Claim 7 fails to comply with 37 CFR 1.75(b). The claim recites the limitation "the adjuvant is coencapsulated with the antigen in the microsphere". However, claim 6 recites the limitation "the adjuvant is encapsulated in the PLGA microspheres". The claims are viewed as duplicates because both claims depend from claim 1 which recites that the antigen is encapsulated within the microspheres.

Claim Rejections - 35 USC § 112

Claims 1, 4-9, and 23-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 was amended to recite the limitation "an essentially homogeneous population" and "beginning at the completion of the second phase". However, the specification does not provide support for these limitation. Although Applicant has indicated that support for "an essentially homogeneous population" is provided especially at page 16, line 27 through page 17, line 32; page 23, lines 27-31; and page 24, lines 17-29. These locations do not appear to recite or suggest the term.

Claim 1 also recites the limitation "the polymer is equal to or less than 1 milliliter per 3 grams of polymer. However, the specification does not provide support for "equal to or less than 1 milliliter per 3 grams" at the pages referred to in Applicant's remarks.

In claims 1 and 23-27, the timing of the second and third phases of the triphasic pattern of antigen release is not enabled. It is stated that the second phase can occur over a period of 30 to 180 days. Since the third phase occurs immediately after the 180 day period, the third phase and the second phase can run anywhere from 190 to 360 days. Support for

this time period is not provided in the specification. Neither page 47, lines 10-15 nor Figure 2 indicates that the second phase occurs at the completion of the first phase. Furthermore, page 59, lines 17-18 indicates that the second burst occurs "between 30 to 65 days in vitro".

In claims 1 and 23-27, the timing of the release of antigen in the second phase is considered new matter. The claims were amended to recite a release over a period of about 30 to 180 days. This time period is not enabled by the specification.

Claim 1 also recites the release of 0.5 to 30% of the antigen released in the initial burst. This is also not enabled by the specification. Applicant refers to Figure 8. However, Figure 8 provides no clear indication that 0.5 to 30 percent of the antigen is released over a period of about 1 day. Furthermore, although page 43 recites that "[T]hese microsphere preparations also did not have a large initial burst (less than 30%, Table 5)," there is no indication that the initial burst was over a period of "about 1 day".

Claims 1, 4-9, and 23-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 the timing of the second and third phases of the triphasic pattern of antigen release is not clear because both the second and third phases have the same range of release (i.e. 1 to 180 days). Since no antigen may be released (0%) during the second phase, the release appears to be biphasic rather than triphasic. Therefore, although a triphasic response is recited in the claim, the timing of the release is not clearly set forth in the claim.

Claim 1 recites the limitation "the" ratio of lactide to glycolide, "the" volume of aqueous antigen, "the" inherent viscosity, and "the" median diameter. However, there is insufficient antecedent basis for these limitations in the claim.

Claim 4 recites the limitation "the" median diameter. However, there is insufficient antecedent basis for this limitation in the claim.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the

patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation of the second phase occurring over a period of between about 30 to 180 days, and the claims 23-27 also recite that the second phase is over a period of about 30 days, 60 days, 90 days, 120 days, and 180 days, respectively which is the narrower statement of the range/limitation.

Claim Rejections

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 9, and 23-27 are rejected under 35 U.S.C. 103 as being unpatentable by Eppstein et al.

Eppstein et al (US Patent #4,962,091) teach a composition comprised of poly(lactide-co-glycolide)(PLGA) with a molar ratio of lactide to glycolide units of 100:0 to 30:70, and an intrinsic viscosity from about 0.2 dl/g to about 1.5 dl/g. Eppstein et al also teach that the composition of PLGA can be used to deliver biologically active polypeptides to mammals. Furthermore, Eppstein et al teach that since the controlled release device produces only minor loss of biological activity of the polypeptides, the likelihood of undesirable immune response at the site of polypeptide delivery is reduced. In addition, Eppstein et al teach that the system can be designed to deliver the active agent at an appropriate rate over prolonged periods of time ranging from less than one day to several months. (See especially column 2, lines 57-61; column 3, lines 32-41, and 60-63; column 4, lines 15-28; column 6; column 11; column 12, lines 31-46)

Although Eppstein et al do not teach a median diameter of the microspheres being from about 20 to 100 um, the reference teaches that the rate and duration of release can be varied by the choice of polylactide polymer, molar ratio, intrinsic viscosity and by the shape and configuration of the device.

Furthermore, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. See In re Aller, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955).

Therefore, absent evidence to the contrary, the median diameter of the microsphere from about 20 to 100 um is considered routine experimentation.

Therefore, it would have been obvious to one of ordinary skill at the time the invention was made to encapsulate antigens within microspheres of various diameters, compositions, and viscosity in order to deliver the antigen for release at various rates and duration with a reduced likelihood of undesirable immune response at the site of delivery.

Claims 1, 4, 9, and 23-27 are rejected under 35 U.S.C. 103 as being unpatentable by Sanders et al in view of Eldridge et al (Mol Immun) and further in view of Jeffery et al.

Sanders et al (J. Pharm. Sci 73(9):1294-1297, 1984) teach a composition comprising poly (D-L-co-glycolide)(PLGA) microspheres and an encapsulated analogue of luteinizing hormone releasing hormone. (See especially page 1294-1296)

Sanders et al also teach that the microspheres have a triphasic release over 90 days in which an initial burst is followed by a latent period of 25 days during which less than 0.4 ug/day of the analogue is released, followed by a final release from about day 38 to day 90 as the polymer erodes (Figure 4(a); pages 1296-1297). However, Sanders et al do not specifically teach the incorporation of an antigen in the microspheres.

Eldridge et al (Mol Immunology 28(3):287-294, 1991) teach the use of PLGA as a safe vaccine delivery system that can control the time and/or rate at which the incorporated material is released which allows for scheduling of the antigen release in such a manner as to maximize the antibody response following a single administration (page 290, column 2, second paragraph). However, Eldridge et al do not teach that various volumes of aqueous antigen can be incorporated into the microsphere.

Jeffery et al (Pharmaceutical Research 10(3):362-8, 1993 (March)) teach a poly (lactide-co-glycolide)(PLGA) microsphere with an entrapped antigen (ovalbumin). (See especially page 263; Abstract)

Several ratios of antigen to polymer (including 1:3) were disclosed by Jeffery et al. The ovalbumin (OVA) was mixed in distilled water before being incorporated into the microsphere.

Jeffery et al disclose several internal aqueous phase volumes. These were achieved by dissolving a constant weight of 60 mg of OVA in distilled water of volumes of 0.5, 1.0, 11.5, and 2.0 mL. (See especially page 363, Preparation of PLG Microparticles with Entrapped Ovalbumin)

The combined teachings of the prior art suggests to a person of skill in the art that compositions containing various volumes of antigen can be encapsulated into microspheres for controlled release of the antigen.

It would have been obvious to include microsphere populations of different characteristics such as different ratios of lactide to glycolide or different sizes in the vaccine composition because the antibody titer from two different populations may be more than additive as disclosed by Eldridge et al. The encapsulation of at least three populations of microspheres with different antigens would also provide the additional convenience in administering multivalent vaccines, such as measles-mumps-rubella or diphtheria-pertussis-tetanus, to children.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use various volumes of antigen incorporated into PLGA (as taught by

Jeffery et al) to produce vaccine preparations with different concentrations of antigens that can be released over a variety of time periods (as taught by Sanders et al in view of Eldridge et al).

Claims 5-7 are rejected under 35 U.S.C. 103 as being unpatentable by Sanders et al, Eldridge et al, and Jeffery et al (as applied to claims 1, 4, 9, and 23-27), and further in view of Wang et al.

The teachings of Sanders et al, Eldridge et al and Jeffery et al were set forth above. It would have been obvious to substitute the analogue of luteinizing hormone releasing hormone in the microspheres taught by Sanders et al with an antigen as disclosed by Eldridge et al and to use the composition as a vaccine for the reasons discussed above.

However, the references differ in not teaching the microsphere composition with an adjuvant.

Wang et al (J. Controlled Release 17:23-32, 1991) teach that PLGA microspheres in which bovine serum albumin (BSA) and the adjuvant Carbopol 951 were encapsulated had a higher burst effect release of the BSA and higher daily release of BSA than the microspheres without Carbopol 951. Wang et al also teach that

Carbopol 951 was incorporated as a potential adjuvant and to enhance protein loading. (See especially page 28, Figure 41; page 29, columns 1 and 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to encapsulate an adjuvant in the antigen-encapsulated microspheres taught in the prior art because the adjuvant would be expected to enhance the immune response of the vaccine composition and may also have the added advantage of a higher initial release of the antigen and more efficient protein loading as taught by Wang et al.

Claim 8 is rejected under 35 U.S.C. 103 as being unpatentable by Sanders et al, Eldridge et al, and Jeffery et al (as applied to claims 1, 4, 9, and 23-27), and further in view of Newman et al.

The teachings of Sanders et al, Eldridge et al, and Jeffery et al were set forth above. It would have been obvious to substitute the analogue of luteinizing hormone releasing hormone in the microspheres (as taught by Sanders et al) with an antigen (as taught by Eldridge et al) and to use the composition as a vaccine for the reasons discussed above. It would also have been

obvious to include an adjuvant in the composition for the reasons discussed above.

The references, however, differ in not teaching the use of QS21 as the adjuvant.

Newman et al teach that QS21 has the advantages of augmenting both antibody responses and cell-mediated immunity and established immunological memory. (See especially pages 146, column 2; and page 1417, paragraph 1)

Given the teachings of the prior art that QS21 is non-toxic and augments both antibody responses and cell-mediated immunity, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include QS21 as an adjuvant in the vaccine composition taught by the above cited references since QS21 can be used as a safe adjuvant in vaccine compositions for establishing immunological memory.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to V. Ryan whose telephone number is (703)305-6558.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Papers related to this application may be submitted to the Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax number for Art Unit 1641 is (703)308-4242.

V. Ryan
Patent Examiner/Art Unit 1641
June 1998
Ryan/vr

JAMES C. HOUSEL 6/22/98
SUPERVISORY PATENT EXAMINER